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EXAMINER	
HA, JULIE	

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,680	WANG ET AL.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,8-22,26,27,29,30,34-38,40,44-51 and 54-67* is/are pending in the application.

4a) Of the above claim(s) *9,14,21,27,47 and 54-65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 8, 10-13, 15-20, 22, 26, 29-30, 34-37, 40, 44-45, 48-51 and 66-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment after Non-final office action filed on July 7, 2008 is acknowledged. Claims 6-7, 23-25, 31-33, 42-43, and 52-53 have been cancelled and new claims 66-67 have been added. Claims 1, 3, 8-22, 26-27, 29-30, 34-38, 40, 44-51, and 54-67 are pending in this application. Claims 9, 14, 21, 27, 47, 54-65 remain withdrawn from further consideration as being drawn to nonelected species. Claims 1, 3, 8, 10-13, 15-20, 22, 26, 29-30, 34-37, 40, 44-45, 48-51 and 66-67 are examined on the merits in this office action.

Withdrawn Rejection

1. Rejection of claims 23-26 and 29-33 under 35 U.S.C. 103(a) as being unpatentable over Pan et al (WO 01/23420) as applied to claims 17-18 and 22 in further view of Edmondson et al (US Patent No. 7,125,873) is hereby withdrawn in view of Applicant's amendment to the claims and submission of statement by the Attorney under 35 U.S.C. 103(c) of common ownership. Rejection under 35 U.S.C. 103(a) of Edmondson et al (US Patent No. 7,125,873) in view of Pallenberg et al (US Patent No. 5,538,945) has been combined and revised in a new rejection below.

Maintained Rejection

35 U.S.C. 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 1, 3, 34-35, 40 and 66-67 are rejected under 35 U.S.C. 102(e) as being anticipated by Edmondson et al (US Patent No. 7,125,873, Provisional Application filed Jul. 6, 2001).

4. The instant claims are drawn to stabilized peptide formulation comprising PACAP 66 or a salt thereof, a transition metal salt and a pharmaceutically acceptable organic solvent.

5. Edmondson et al teach a pharmaceutical composition comprising compound of Formula II) and consisting of other group, including PACAP receptor 3 agonist (the same peptide sequence as SEQ ID NO:1 of instant application) and a pharmaceutically acceptable carrier (see column 12, lines 44-47, column 13, lines 3-4 and claim 1). The reference further teaches that the term “pharmaceutically acceptable salt” refers to salts prepared from pharmaceutically acceptable bases or acids including inorganic or organic bases and acids…copper…zinc and the like (see column 6, lines 45-51). This meets the limitations of claims 1, 3, 34-35, 40 and 66-67. The reference further teaches that the pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension...in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol (see column 15, lines 60-67 and column 15, lines 1-5). Since the instant claims are drawn to an open-ended “comprising”, this

implies that there may be other components in the formulation. Furthermore, the reference teaches that the injectable pharmaceutical composition comprising the PACAP 66, the metal salt (zinc) and organic solvent, the peptide formulation is stable.

Response to Applicant's Arguments

6. Applicant argues that "the office action reconstructs the recited components of the claimed formulation by picking and choosing each of the recited components of the instantly claimed formulation; i.e., the peptide component, the metal salt component and the organic solvent component, from three separate "laundry lists" disclosed by Edmonson et al without respect to the claimed property that the peptide formulation be stabilized." Applicant further argues that "Edmondson et al. does not specifically cite the instantly recited peptide PACAP 66…the office action selects the salt component of the formulation from an extensive list of salts disclose in a definition of the tem in Edmonson et al. that generically includes zinc salts. Zinc salts are not even included in Edmondson's preferred embodiments, providing further support that Edmondson et al. is not specifically considering the claimed formulation comprising a zinc salt." Furthermore, Applicant argues that "there is no recognition in Edmondson regarding the stability of the peptide. In contrast, the instant specification teaches that the stability of PACAP 66 is less than that of other typical peptides."

7. Applicant's arguments have been fully considered but have not been found persuasive. Applicant is reminded that the claims are drawn to an open-ended transitional phrase "comprising". This implies that there are other components in the

formulation. Edmondson reference teaches 14 different classes ((a)-(n), see columns 12-13) of active ingredients that may be administered in combination with a compound of Formula I. These class of compounds can be at once envisaged in combination with compound of Formula I. The MEP states the following: “If one of ordinary skill in the art is able to "at once envisage" the specific compound within the generic chemical formula, the compound is anticipated." (see MPEP 2131.02). Furthermore, these class of compounds are recited in the claims of the reference (see claim 1, for example). Therefore, the compounds are clearly anticipated by the reference. In regards, Applicant’s argument that “the office action selects the salt component of the formulation from an extensive list of salts disclosed in a definition of the term in Edmonson et al. that generically includes zinc salts" and "Zinc salts not even included in Edmondson's preferred embodiments", Edmondson reference lists 14 different salts that are pharmaceutically acceptable. Again, one of ordinary skilled in the art is able to "at once envisage" the zinc salt in the formulation. A preferred embodiment of a reference does not teach away from the instantly claimed invention. The MPEP states the following: “A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments…reference disclosing optional inclusion of a particular component teaches compositions that both do and do not contain that component...” (see MPEP 2123 [R-5]). It should be noted Applicant is reciting broad organic solvents in the broad claim 1. In the specification, Applicant discloses that "the organic solvent is preferably DMSO, 1-methyl-2-pyrrolinidone or propanol" (see paragraph [0”08] of instant

specification US 2005/0009739 A1). Applicant would not agree that organic solvents is limited to the preferred embodiments. Since there are 14 transition metal pharmaceutically acceptable salts listed, one of ordinary skill in the art would necessarily use any of the 14 salts. Since the PACAP 66 and the zinc salt and a pharmaceutically acceptable organic solvent is present in the composition, it would necessarily be stable, meeting the limitations of the instant claims.

35 U.S.C. 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Edmondson et al (US Patent No. 7,125,873).

12. The instant claim is drawn to a stabilized peptide formulation comprising PACAP66, $ZnCl_2$, and pharmaceutically acceptable organic solvent.

13 The teachings of Edmondson et al are described, supra. The difference between the reference and the instant claim is that the reference does not teach $ZnCl_2$.

14. As described above, Edmondson teaches that the term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable bases or acids including inorganic or organic bases and inorganic or organic acids...copper...zinc and the like.

15. Therefore, it would have been obvious for one of ordinary skill in the art to use pharmaceutically acceptable organic or inorganic salts in the formulation to produce a stabilized peptide formulation. One of ordinary skill in the art would have been motivated to use $ZnCl_2$, since it is pharmaceutically acceptable salt that is used in pharmaceutical compositions that are in an injectable or oleaginous suspension. There is a reasonable expectation of success, since zinc salts are readily available, and pharmaceutically acceptable salt that is used in pharmaceutical compositions for parenteral administration purposes.

Response to Applicant's Arguments

16. Applicant argues that "Edmondson et al does not teach the instantly claimed peptide formulation. Zinc salts are not even included in Edmondson's preferred embodiments of pharmaceutically acceptable salts, being disclosed only in a laundry list of salts." Furthermore, Applicant argues that "in view of this surprising instability of the PACAP 66 peptide, and that the salt of the transition metal zinc was not listed as a preferred pharmaceutically acceptable salt by Edmondson et al. one of ordinary skill in the art at the time of the invention would not have had a reasonable expectation of success in achieving the claimed peptide formulation."

17. Applicant's arguments have been fully considered but have not been found to be persuasive. Edmondson reference teaches 14 different classes ((a)-(n), see columns 12-13) of active ingredients that may be administered in combination with a compound of Formula I. In regards, Applicant's argument that "the office action selects the salt component of the formulation from an extensive list of salts disclosed in a definition of the term in Edmonson et al. that generically includes zinc salts" and "Zinc salts not even included in Edmondson's preferred embodiments", Edmondson reference lists 14 different salts that are pharmaceutically acceptable. Again, one of ordinary skilled in the art is able to "at once envisage" the zinc salt in the formulation. A preferred embodiment of a reference does not teach away from the instantly claimed invention. The MPEP states the following: "A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred

embodiments…reference disclosing optional inclusion of a particular component teaches compositions that both do and do not contain that component..." (see MPEP 2123 [R-5]). It should be noted Applicant is reciting broad organic solvents in the broad claim 1. In the specification, Applicant discloses that "the organic solvent is preferably DMSO, 1-methyl-2-pyrrolinidone or propanol" (see paragraph [0"08] of instant specification US 2005/0009739 A1). Applicant would not agree that organic solvents is limited to the preferred embodiments. Therefore, it would have been obvious to one of ordinary skill in the art to use a commercially available $ZnCl_2$ salt to formulate a peptide formulation.

18. Claims 44-46, 48-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohsaki et al (US Patent No. 5,428,129) in view of Thakur (US 2003/0129133 A1) and Edmondson et al (US Patent No. 7125873).

19. The instant claims are drawn to a method for preparing a stabilized peptide formulation.

20. Ohsaki et al teach the method of preparing peptide formulation. The reference teaches that Boc-Ser(Bzl)-Asn-Leu-Opac (2.11 g) was dissolved in 7 ml of TFA under ice-cooling and the solution was allowed to stand at room temperature for 1 hour. The solution was then ice-cooled again and 4 N HCl/dioxane (2.5 ml) was added. After shaking, the mixture was treated with diethyl ether and the resulting precipitate was collected by filtration and dried under reduced pressure over potassium hydroxide (see column 27, lines 56-58). The reference further teaches that SEQ ID NO:1 was

lyophilized to give purified compound (see Example 3). Since the reference teaches that SEQ ID NO:1 was lyophilized, it is inherent that other SEQ ID NOS would also be lyophilized to recover the purified compound. Although the prior art is silent as to cooling the acid solution below room temperature, it is inherent that the acid solution is cooled to the same temperature as the peptide to keep the reaction under the same condition. Additionally, the prior art recites HCl/dioxane solution mixing with the peptide. It is inherent that HCl is made up of mixture of water and acid, therefore, recitation of HCl in the prior art meets the limitation of acid solution of acid and water. The difference between the reference and the instant claims is that the reference does not teach PACAP 66 and transition metal salt.

21. However, Thakur teaches method of producing biologically active PACAP or its PACAP fragment or analog (see abstract). The reference teaches that PACAP can be synthesized de novo using conventional solid phase synthesis methods. The peptide chain is prepared by a series of coupling reactions…various active esters…TFA, HCl in dioxane…reaction in solution with isolation and purification are well known in the art (see paragraph [0068]).

22. Edmondson et al teach pharmaceutical composition comprising PACAP receptor 3 agonist (same sequence as SEQ ID NO:1 of the instant application) and a pharmaceutically acceptable carrier and pharmaceutically acceptable salt, including inorganic or organic bases and inorganic or organic acids…copper, zinc and the like (see column 6, lines 45-51). The reference teaches that the PACAP 66, the metal salt and organic solvent peptide formulation is stable. The reference teaches that when the

compound of the invention is basic, salts may be prepared from pharmaceutically acceptable acids, including inorganic and organic acids…acetic, hydrochloric…phosphoric (see column 7, lines 1-11).

23. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Ohsaki et al, Thakur and Edmondson et al because each prior art teaches formulation comprising peptides used in treatment of diseases or disorders. There is a motivation to combine, since Ohsaki teaches the method of preparing the stable peptide of a 31mer as well as other peptides, and Thakur teaches similar methods for the PACAP and its analogs, and Edmondson et al teach PACAP 66 and transition metal formulation that can also be prepared with pharmaceutically acceptable acids (inorganic and organic acids). There is a reasonable expectation of success since Ohsaki et al teach a 31 mer peptide having the sequence SNLSTXVLGKLSQELHKLQTYPRTDVGAGTP being prepared in such steps, being utilized for pharmaceutical compositions. Therefore, one of ordinary skilled in the art would expect to achieve the same results for a 31 mer having the sequence HSDAVFTDNYTRLRKQVAAKKYLQSIKNKRY (PACAP 66), since a 31mer and other peptides having different lengths were prepared in the same manner. There is a reasonable expectation that the 31mers would at least react the same way to the process conditions. Furthermore, it has been held that under KSR that “obvious to try” may be an appropriate test under 103. The Supreme Court stated in KSR, When there is motivation “to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within

his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727,_,82 USPQ2d 1385, 1397 (2007).

24. The "problem" facing those in the art was developing novel polypeptides that function as agonists in vivo that are effective in treatment of diseases and conditions, and there were a limited number of methodologies available to do so, for example trying different acids, bases and salts and different pharmaceutically acceptable organic solvents. The pharmaceutically acceptable organic solvents are commercially available and limited in selection, it would have been obvious to try different organic solvent to produce the most active final peptide composition. The skilled artisan would have had reason to try these methodologies with the reasonable expectation that at least one would be successful. In this case, both prior arts teach the use of organic acids (acetic) and Edmondson et al teach that inorganic acids may also be used. Thus, producing a peptide formulation using inorganic acids, such as hydrochloric and phosphoric and pharmaceutically acceptable organic solvents such as DMSO, is a "the product not of innovation but of ordinary skill and common sense," leading to the conclusion that invention is not patentable as it would have been obvious.

25. Regarding the molar ratio of inorganic acid to peptide, it would have been obvious to optimize the molar ratio of acid to peptide to achieve the optimal final product. The MPEP states the following: Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the

prior art unless there is evidence indicating such concentration or temperature is critical. *"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."* *In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)* (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("*The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.*"); *In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969)* (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. Denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). One of ordinary skill in the art would have tried different concentrations of organic solvent and different molar ratios of inorganic acid to peptide to produce the optimal, final product that has the highest activity, stability and purity. Therefore, there is a reasonable expectation of

success, since the normal desire of artisans is to improve upon the conditions already known.

Response to Applicant's Arguments

26. Applicant argues that "PACAP 66 is a particularly unstable peptide, and thus one of skill would not have had a reasonable expectation of success in arriving at the claimed invention at the time of the invention." Applicant further argues that "in view of the generic teachings of Edmondson regarding pharmaceutical compositions, the combination of references does not render the instant claims obvious."

27. Applicant's arguments have been fully considered but have not been found persuasive. Ohsaki et al teach the method of preparing peptide formulation and Thakur teaches that PACAP and its analogs can be prepared using de novo synthetic methods. Ohsaki teaches the method of preparing stabilized peptide formulation of 31mer and other peptides that have been synthesized using conventional synthesis methods. Edmondson teaches a stabilized peptide formulation that includes PACAP 66, zinc salt and organic solvent. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of the prior arts, since they teach stabilized peptide formulation. One of ordinary skill in the art would have been motivated to try the combining the teachings of Ohsaki, Thakur and Edmondson to optimize the PACAP 66 peptide formulation, to optimize the stability conditions to arrive at the most optimal, stable peptide formulation. Since other peptides having longer residues, such as a 31mer was stable using the Ohsaki method, one would at least expect that the combing

the prior arts would at least result in a peptide formulation that is as stable as the Ohsaki peptides.

Revised Rejection-35 U.S.C. 103

28. (Revised, New) Claims 1, 3, 8, 10-13, 15-20, 22, 26, 29-30, 34-37, 40 and 66-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edmondson et al (US Patent No. 7,125,873) in view of Pallenberg et al (US Patent No. 5,538,945) and Maccecchini (US Patent No. 5,830,998, filed with IDS) and Bolin (US Patent No. 5,234,907, filed with IDS) and Igari et al (US 2002/0058622 A1).

29. The teachings of Edmondson et al is described, supra. The difference between the reference and the instant claims is that the reference does not teach DMSO as organic solvent, the molar ratio, the concentration of PACAP 66, and the inorganic acid.

30. However, Pallenberg et al teach peptide-copper complexes that may be formulated for administration (topical or injection) to contain additional ingredients such as penetration enhancement agents and/or surface active agents, such as DMSO (see abstract and column 9, lines 1-4 and 15-18). Pallenberg further teaches that the peptide is lyophilized (see Examples).

31. Maccecchini teaches a stable peptide formulation comprising a pharmaceutically acceptable organic solvent and physiologically acceptable divalent metal ion (a transition metal salt) such as zinc, manganese, calcium and mixture thereof, and organic solvents such as propylene glycol and polyethylene glycol (see column 16).

32. Bolin teaches the use of various organic and inorganic solvents including HCl and TFA in a process of stabilizing peptide formulation and a lyophilization process thereof (see Examples).

33. Igari et al teach a sustained release preparation comprising a water-insoluble or slightly water-soluble polyvalent metal salt of a water-soluble physiologically active substance (see abstract). Igari teaches that the physiologically active substance is RGDS, PACAP, and so on (see paragraph [0058]). The polyvalent metal is transition metals (e.g., iron (II), copper (II), zinc (II), etc) (see paragraph [0059]) and that the polyvalent metals and inorganic acids are zinc chloride, calcium chloride, sulfates, nitrates, thiocyanates (see paragraph [0071]).

34. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Edmondson et al, Pallenberg et al, Maccecchini, Bolin and Igari references, to formulate a stabilized peptide formulation in DMSO and transition metal salts. One of ordinary skill in the art would be motivated to add in DMSO as organic solvent, since DMSO is a penetration enhancement agent that are used in topical and injection formulations. There is a reasonable expectation of success, since Edmondson et al teach the formulation in 1,3-butane diol (non-toxic parenterally-acceptable diluent), and DMSO is readily available solvent that is used to enhance penetration, and is safe for topical and injection usage (pharmaceutically acceptable).

35. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Edmondson et al, Pallenberg et al, Maccecchini, Bolin and Igari, to formulate a stabilized peptide formulation in DMSO and $ZnCl_2$ salt. One of

ordinary skill in the art would be motivated to substitute the one organic solvent with another, since DMSO is a penetration enhancement agent that are used in topical and injection formulations. Furthermore, it would have been obvious for one of ordinary skill in the art to use pharmaceutically acceptable organic or inorganic salts in the formulation to produce a stabilized peptide formulation. One of ordinary skill in the art would have been motivated to use $ZnCl_2$, since it is pharmaceutically acceptable salt that is used in pharmaceutical compositions that are in an injectable or oleaginous suspension. Furthermore, Edmondson reference and Igari reference teach zinc and copper transition metal salts, thus one would try one for the other. There is a reasonable expectation of success, since zinc salts are readily available, and pharmaceutically acceptable salt that is used in pharmaceutical compositions for parenteral administration purposes. There is a reasonable expectation of success, since Edmondson et al teach the formulation in 1,3-butane diol (non-toxic parenterally-acceptable diluent), and DMSO is readily available solvent that is used to enhance penetration, and is safe for topical and injection usage (pharmaceutically acceptable). Furthermore, it would have been obvious to lyophilize the peptide formulation for longer storage and lyophilized peptide formulation can be easily resuspended for administration.

36. Regarding the molar ratio of $ZnCl_2$ to peptide, the concentration of PACAP to organic solvent, it would have been obvious to optimize the molar ratio and peptide concentration to solvent to achieve the optimal final product through routine experimentation. The MPEP states the following: Generally, differences in concentration

or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. *"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."* In re Aller, *220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)* (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("*The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.*"); In re Hoeschele, *406 F.2d 1403, 160 USPQ 809 (CCPA 1969)* (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). One of ordinary skill in the art would have tried different concentrations of organic solvent and different molar ratios of salt to peptide to produce the optimal, final product that has the highest activity, stability and

purity. Therefore, there is a reasonable expectation of success, since the normal desire of artisans is to improve upon the conditions already known through routine experimentation.

Response to Applicant's Arguments

37. Applicant argues that "Pallenberg reference teaches DMSO may be used in peptide copper complexes formulated for administration." Applicant argues that "Pallenberg's teaching is inapplicable to the claimed formulation, especially in light of the particular instability of the PACAP 66 peptide as disclosed in the specification."

38. Applicant's arguments have been fully considered but have not been found persuasive. Edmondson reference teaches 14 different classes ((a)-(n), see columns 12-13) of active ingredients that may be administered in combination with a compound of Formula I. In regards, Applicant's argument that "the office action selects the salt component of the formulation from an extensive list of salts disclosed in a definition of the term in Edmonson et al. that generically includes zinc salts" and "Zinc salts not even included in Edmondson's preferred embodiments", Edmondson reference lists 14 different salts that are pharmaceutically acceptable, including copper and zinc. Again, one of ordinary skilled in the art is able to "at once envisage" the zinc salt in the formulation. A preferred embodiment of a reference does not teach away from the instantly claimed invention. The MPEP states the following: "A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments…reference disclosing optional inclusion of a

particular component teaches compositions that both do and do not contain that component..." (see MPEP 2123 [R-5]). It should be noted Applicant is reciting broad organic solvents in the broad claim 1. In the specification, Applicant discloses that "the organic solvent is preferably DMSO, 1-methyl-2-pyrrolinidone or propanol" (see paragraph [0"08] of instant specification US 2005/0009739 A1). Applicant would not agree that organic solvents is limited to the preferred embodiments. Therefore, it would have been obvious to one of ordinary skill in the art to use a commercially available $ZnCl_2$ salt to formulate a peptide formulation, since Edmondson reference teaches 14 transition metal salts including zinc and copper; Igari reference teaches a sustained release peptide (PACAP) comprising polyvalent salts that are iron (II), zinc (II) or copper (II). One of ordinary skill in the art would have been motivated to try zinc salt for a copper salt, since Edmondson and Igari teach that these salts are used in pharmaceutical formulations and Igari teaches that the formulation is for sustained release of pharmaceutically active agents (PACAP).

Conclusion

39. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/J. H./
Examiner, Art Unit 1654

/Anish Gupta/
Primary Examiner, Art Unit 1654